REMARKS

Review and reconsideration on the merits are requested.

Basis for Claim Amendments; New Claim

Claim 1 finds basis at page 7, lines 21-22 and claim 28 finds basis at page 22, line 9.

The Prior Art

U.S. 5,387,603 Kitazawa et al (Kitazawa); U.S. 2002/0177593A1 Ishihara et al (Ishihara); U.S. 4,757,090 Salpekar (Salpekar); U.S. 5,370,878 Shah (Shah).

Claim Rejections - 35 U.S.C. § 103

Claims 1, 8, 9, 11, 12 and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kitazawa in view of Ishihara and in further view of Salpekar and Shah.

The Examiner's position is set forth in the Action and will be repeated here only as necessary to an understanding of Applicants' traversal which is now presented.

Submission of DECLARATION...1.132

In view of the Examiner's criticisms of the DECLARATION...1.132 of record, Applicants submit herewith a further DECLARATION...1.132 signed by Declarant Naganuma on June 23, 2009.

Traversal

The Capsule of the Present Invention

The capsule of the present invention exhibits an excellent immediate dissolution property in water in which the active ingredient, KMD-3213, is hardly soluble. The capsule of the present invention also has excellent therapeutic activity for the treatment of dysuria. The capsule of the

present invention further has excellent storage stability, has good manufacturing capability without filling problems during the encapsulating process and provides high content uniformity. The capsule of the present invention is eminently suitable for industrial production.

Kitazawa

Kitazawa merely discloses the compound KMD-3213 and its use as a therapeutic agent for treating dysuria. See cols. 49 to 50, Compound 40 in Kitazawa. Kitazawa fails to teach or suggest the capsule of the present invention or the advantageous effects of the capsule of the present invention.

Ishihara

The invention of Ishihara is directed to agents for improving the excretory potency of the urinary bladder. Ishihara discloses several Formulation Examples on page 51, and pages 55 to 56 as Formulation Examples 1 to 6 in the Ishihara specification. The formulations are all tablets containing a) lactose, b) corn starch and c) magnesium stearate. The dosage forms and compositions of Formulation Examples 1 to 6 are all quite different from those of the capsule of the present invention.

Ishihara also discloses in a general fashion Formulations, Administration Routes and Dosages on pages 43 to 46. Ishihara teaches a variety of organic or inorganic carrier materials conventionally employed as pharmaceutical materials such as bulking agents, lubricants, binders, and disintegrators for solid preparations. A number of examples of bulking agents, lubricants, binders, disintegrators are listed in the Ishihara specification.

However, Ishihara does not specifically disclose the capsule of the present invention. Ishihara also fails to teach or suggest what kind of bulking agents, lubricants or disintegrators could provide capsules containing KMD-3213 with immediate dissolution properties, excellent storage stability, and good manufacturing capability. Ishihara does not teach or suggest the advantageous effects of the capsule of the present invention in any fashion.

Salpekar

The invention of Salpekar is directed to an N-acetyl-p-aminophenol composition containing pregelatinized starch useful in direct tabletting.

Salpekar discloses a particulate N-acetyl-p-aminophenol composition comprising as components:

(a) from about 84 to 94 percent, based on the dry weight of the composition, of N-acetyl-p-aminophenol,

(b) from about 5 to about 15 percent, based on the dry weight of 'the composition, of a pharmaceutically acceptable pregelatinized starch, and

(c) water.

Salpekar discloses several directly tabletable granular compositions as Examples I to IV. However, the compositions of Examples I to IV are all quite different from those of the capsule of the present invention.

Salpekar teaches:

"The pregelatinized starch is included in an amount effective for imparting to the composition the capability of being formed into tablets having high hardness, short disintegration

time (e.g., about 10 minutes or less) and short dissolution time (e.g., about 20 minutes or less for 80 percent or more of APAP to dissolve)" on col. 2, lines 60 to 66 of the Salpekar specification.

Salpeker also teaches (bolding is added):

"The lubricant component may be any pharmaceutically acceptable lubricant, which may be, e.g., hydrophilic or hydrophobic. This component is present in a lubricating amount at least sufficient to impart mold release properties to tablets formed in the compositions and preferably **insufficient to increase disintegration time and dissolution time of such tablets...**"

***

"Suitable lubricants for use as the lubricating component include, for example, stearic acid, metallic stearate (such as sodium, calcium, magnesium and zinc stearate, etc.), sodium lauryl sulfate, polyethylene glycol, hydrogenated vegetable oils, talc and compatible mixtures of two or more such materials. Stearic acid is preferred."

See col. 3, lines 3 to 9 and lines 13 to 18 of the Salpekar specification.

However, Salpekar fails to teach or suggest what combination of a bulking agent, disintegrator and lubricant could provide capsules containing KMD-3213 with excellent immediate dissolution properties and excellent storage stability. Salpekar also fails to teach or suggest how filling problems caused by the cohesive nature of KMD-3213 during encapsulating could be overcome, and what combination of a bulking agent, disintegrator and lubricant could provide capsules comprising KMD-3213 with good manufacturing capability.

Salpekar fails to teach or suggest the capsule of the present invention or the advantageous effects of the capsule of the present invention.

Shah

The invention of Shah is directed to a method for preparing a granulated acetaminophen composition suitable for direct compression into tablets.

Shah discloses a method for preparing a free-flowing particulate granulated acetaminophen composition, which comprises:

(A) blending a mixture of (a) from about 70 to about 95 percent of acetaminophen by dry weight of the blend, (b) from about 1 to about 10 percent of binder by dry weight of the blend, (c) from about 0.5 to about 3 percent of lubricant by dry weight of the blend, (d) from about 0 to about 2 percent of disintegrating agent by dry weight of the blend, and (e) from about 1 to about 7 percent of a liquid selected from the group consisting of water, methanol, ethanol, isopropanol and mixtures thereof by dry weight of the blend;

(B) compacting the blend of Step A to form a compact; and

(C) milling the compact of Step B to form the said granulated acetaminophen composition.

Shah teaches:

"The resultant product is suitable for direct compression into superior tablets with respect to compressibility, hardness, tablet esthetics and rapid disintegration and dissolution times." See the Shah specification at col. 3, lines 56 to 59.

Shah also teaches several lubricants such as stearic acid, stearate salts such as calcium, magnesium and zinc stearate, colloidal silica, polyethylene glycol, hydrogenated vegetable oils, talc and combinations thereof. See the Shah specification at col. 4, lines 13 to 16.

However, Shah fails to teach or suggest what combination of a bulking agent, disintegrator and lubricant could provide capsules containing KMD-3213 with excellent immediate dissolution properties and excellent storage stability. Shah also fails to teach or suggest how filling problems caused by the cohesive property of KMD-3213 during encapsulating could be overcome, and what combination of a bulking agent, disintegrator and lubricant could provide capsules containing KMD-3213 with good manufacturing capability.

Shah fails to teach or suggest the capsule of the present invention or the advantageous effects of the capsule of the present invention.

Unobviousness Over the Combination of References

The Examiner states in the Action of January 22, 2009 on pages 2 to 3:

"Salpekar teaches the use of pregelatinized starch for imparting a short dissolution time, i.e. about 20 minutes or less for 80% or more of active compound to dissolve".

However, a comparison of Example 1 and Capsule C of the present invention with Capsules H and B of Comparative Examples in the DECLARATION...1.132 shows that blending partially pregelatinized starch with KMD-3213 in Capsules H and B does not impart immediate dissolution at all. The dissolution rates after 15 minutes of Capsules H and B were only 23% and 8% while those of Example 1 and Capsule C were 93% and 97%.

Further, a comparison of Capsule H with Capsule M shows that blending partially pregelatinized starch in place of corn starch with KMD-3213, makes the dissolution of Capsule H worse.

From the above results, Applicants respectfully submit that one of ordinary skill in the art

would understand that the immediate dissolution property of KMD-3213 cannot be achieved using only partially pregelatinized starch.

The Examiner also states in the Action (paragraph bridging pages 2/3 of the Action) that the comparative example in the 132 DECLARATION submitted on December 1, 2008 (hereafter the December DECLARATION), is improper since Declarant used 22 and 45 times more KMD-3213 in the compositions of the comparative examples.

However, in the dissolution test of the December DECLARATION, Declarant used comparative capsules 1A, 1B, 2A and 2B containing 4.0mg of KMD-3213. It is stated that the mixture was filled into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213 in the paragraph of "Preparation of comparative capsules 1A, 1B, 2A and 2B", each of the comparative capsules contain 4.0mg of KMD-3213. See the December DECLARATION at page 2, line 3 from the bottom of the page and page 3, lines 5 and 6 from the bottom of the page.

Regarding the ratio of KMD-3213 and partially pregelatinized starch to the total weight of compositions, the Examiner is requested to refer to the DECLARATION...1.132 filed March 31, 2008 (the March DELCARATION). These results are again presented in Table 1 at page 4 of the present DECLARATION. In the March 2008 DECLARATION and the present DECLARATION, a comparison is presented of the dissolution rate of Example 1 with that of Capsule H, both of which contain the same amount and ratio of KMD-3213 and mannitol, and partially pregelatinized starch. As discussed above, the results of dissolution tests clearly show that the capsule of Comparative capsule H has a notably lower dissolution rate as compared with that of the capsule of Example 1 of the present invention. It is clear that the general mention of partially pregelatinized starch in

Salpekar does not teach or support the immediate dissolution property exhibited by the present capsules.

Salpekar also teaches:

"The lubricant component may be any pharmaceutically acceptable lubricant, which may be, e.g., hydrophilic or hydrophobic. This component is present in a lubricating amount at least sufficient to impart mold release properties to tablets formed in the compositions and preferably **insufficient to increase disintegration time and dissolution time of such tablets"** See Salpekar at col. 3, lines 3 to 9; bolding added.

In that paragraph, Salpekar only teaches that the use of lubricant components will influence the compositions containing the lubricants to increase their disintegration and dissolution time.

In fact, the dissolution rates of Capsules B and H, containing magnesium stearate as a lubricant, are notably lower as compared with the dissolution rate of Capsule A which does not contain magnesium stearate. The dissolution test on Capsules 1A, 1B, 2A and 2B in the present DECLARATION show that all of these Comparative capsules showed less than 20% dissolution after 15 minutes.

Applicants respectfully submit that the mere glancing and general mention regarding lubricants in Salpekar, fails to teach or suggest what kind of lubricants should be used for providing compositions containing KMD-3213 with excellent immediate dissolution properties.

Shah also teaches several lubricants such as stearic acid, stearate salts such as calcium, magnesium and zinc stearate, colloidal silica, polyethylene glycol, hydrogenated vegetable oils, talc and combination thereof. See Shah at col. 4, lines 13 to 16. As working embodiments, Shah

discloses several tablets formulations as described in Table I, III, V, IX, XI and XIV. All of these formulations contains silicon dioxide as a lubricant.

In light of this disclosure in Shah, Declarant in the present DECLARATION compared Capsule C of the present invention containing sodium lauryl sulfate with Comparative Example F containing silicon dioxide instead of sodium lauryl sulfate as shown in the present DECLARATION. Comparative Example F and Capsule C contained the same amount and ratio of KMD-3213, mannitol, partially pregelatinized starch, magnesium stearate, and silicic acid or sodium lauryl sulfate. The results of dissolution test show that the dissolution rate after 15 minutes of Comparative Example F is only 9% while the dissolution rate of Capsule C is 85%.

Shah fails to teach or suggest what kind of lubricants should be used for providing compositions containing KMD-3213 with immediate dissolution properties.

Ishihara discloses several Formulation Examples on page 51, and pages 55 to 56 as Formulation Examples 1 to 6 in the Ishihara specification. The formulations are all tablets containing a) lactose, b) corn starch and c) magnesium stearate.

Ishihara also teaches a variety of organic or inorganic carrier materials conventionally employed as pharmaceutical materials such as bulking agents, lubricants, binders and disintegrators for solid preparations. A number of bulking agents, lubricants, binders and disintegrators are listed in the Ishihara specification.

In the present DECLARATION, Declarant shows the result of Capsule M containing D-mannitol instead of lactose in the Formulation of Example 1 in Ishihara and also shows the results of Capsule B and H containing partially pregelatinized starch instead of corn starch in Capsule M.

The dissolution test on Capsule M showed a moderate dissolution rate of 64%, but filling problems such as sticking during encapsulating were observed in the manufacture of Capsule M. Therefore, Declarant could not prepare Capsule M on a manufacturing scale. Substituting partially pregelatinized starch for corn starch resulted in an improvement of the filling problem during encapsulating. On the contrary, use of partially pregelatinized starch instead of corn starch made the dissolution of Capsules B and H notably worse.

It is a very difficult technical problem to achieve immediate dissolution properties and good manufacturing capacity without causing filling problems during encapsulating at the same time.

As discussed above, Kitazawa, Ishihara, Salpekar and ShaH fail to teach or suggest how to improve dissolution properties in water, in which KMD-3213 is hardly soluble, and how to resolve filling problems caused by the cohesive property of KMD-3213 during encapsulating at the same time.

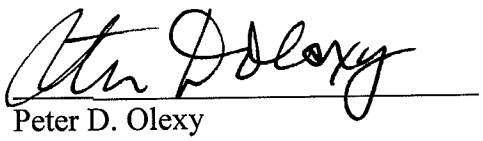
Further, the capsule of the present invention also has the advantageous effects of exhibiting excellent storage stability and a high content uniformity suitable for industrial production.

Withdrawal of the rejection over Kitazawa in view of Ishihara and further in view of Salpekar and Shah is respectfully requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Peter D. Olexy
Registration No. 24,513

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: July 22, 2009